

Computational Prediction of Glass-Forming Ability and Crystallization Tendencies

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Introduction

The amorphous state can be used as a means to overcome poor aqueous dissolution and therefore, early decision tools of the glass-forming ability (GFA) of compounds are warranted. Only a few studies have targeted the molecular properties that drive GFA and physical stability of the amorphous state formed.^{1,2} Molecular weight (MW) of drugs has previously been suggested as a potential descriptor for predicting GFA,² however, no important molecular descriptors for crystallization tendency have been identified.

Aim

To identify molecular properties of importance for GFA and crystallization tendency.

Method

A data set of 100 compounds was used and 284 chemical descriptors were calculated using ADMETPredictor (SimulationsPlus, CA). The responses investigated were i) the ability to form glass (glass-former (GF) or non-glass-former (nGF)) and ii) crystallization tendency of GFs upon heating of undercooled melt. Drug powder was processed by standard DSC melt-quenching to investigate these responses. Compounds that crystallized upon cooling were considered as nGF. GF compounds that crystallized upon heating were sorted as Class II whereas Class III compounds did not show any crystallization tendency when heated.¹

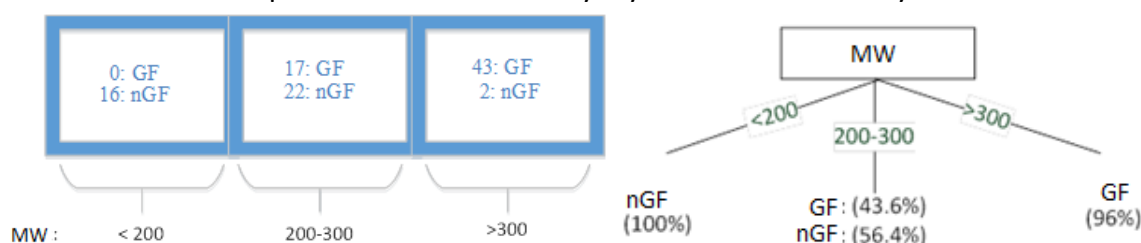


Fig. 1. The number of compounds in each group (left) and the accuracy of MW to separate between GF and nGF (right).

Results

MW in the range from 200 to 300 was a poor predictor of GFA (Fig. 1). The statistical methods identified two additional descriptors reflecting pi Fukui indices and aromatic ring structures which together with MW accurately predicted 86% of GF and 80% of nGF in the range from 200 to 300. A single descriptor reflecting the Sum of absolute values of Hückel pi atomic charges for C atoms could predict Class II and Class III with an accuracy of 79% and 95%, respectively. The models were currently evaluated with test sets to explore the general applicability.

Conclusion

Glass-forming ability and crystallization tendencies could be predicted with high accuracy from rapidly calculated molecular descriptors.

References

1. Baird, J. A et al. J Pharm Sci (2010) 99: 3787-3806.
2. Mahlin, D et al. Eur. J. Pharm. Sci., (2013) 49: 323–332.